

Mucosal lesions of the gastric mucosa in adult patients with coeliac disease

Zmiany w błonie śluzowej żołądka u dorosłych chorych na celiakię

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Słowa kluczowe: celiakia, limfocytarne zapalenie żołądka, dyspepsja.

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Abstract

Introduction: Coeliac disease is a chronic inflammatory disorder of the gastrointestinal tract, of autoimmune etiology, in genetically predisposed persons. The role of the gastric lesions and their influence on the clinical course of that disease have not been explained.

Aim: To evaluate the frequency of morphological lesions in the gastric mucosa in adults with coeliac disease and their effect on the clinical picture of gluten enteropathy.

Material and methods: Ninety patients, including 35 patients with coeliac disease and 55 with dyspeptic symptoms (control group) were examined. Clinical studies comprised history of disease, physical examination, blood tests and gastroscopies. Biopsies from the gastric and distal part of the duodenal mucosa were stained with haematoxylin-eosin, for estimation of the intensity of mucosal changes and a count of the intraepithelial lymphocytes (IEL). Immunohistochemical studies with anti-CD3 antibodies were performed for the identification of CD3⁺ lymphocytes.

Results: An increased number of IEL was observed in coeliac patients treated as well as not treated with gluten, compared with the control group. Lymphocytic gastritis (LG) was observed in 8.6% of coeliac patients. Patients with coeliac disease and LG presented intense dyspeptic symptoms. Presence of CD3⁺ T lymphocytes was revealed in the gastric and duodenal mucosa with immunohistochemical staining.

Conclusions: Morphological lesions in the gastric mucosa belong to gastroenteropathy in the course of coeliac disease and may induce dyspeptic symptoms. Taking biopsies from the distal part of the duodenum in patients with dyspeptic symptoms should be considered.

Streszczenie

Wstęp: Celiakia jest przewlekłą chorobą zapalną przewodu pokarmowego o podłożu autoimmunologicznym, występującą u osób predysponowanych genetycznie. Znaczenie zmian patologicznych w błonie śluzowej żołądka u chorych na celiakię i ich wpływ na przebieg kliniczny tej choroby nie zostały dotąd w pełni poznane.

Cel: Ocena częstości występowania zmian histopatologicznych w błonie śluzowej żołądka u dorosłych osób z celiakią oraz wpływu tych zmian na obraz kliniczny choroby.

Materiał i metody: Do badań włączono 90 pacjentów, w tym 35 chorych na celiakię i 55 osób z objawami dyspeptycznymi (grupa kontrolna). Obejmowały one wywiad chorobowy, badanie przedmiotowe, badania krwi oraz panendoskopię. Wykinki z błony śluzowej żołądka i części pozaopuszkowej dwunastnicy barwiono hematoksyliną i eozyną. Oceniano nasilenie zmian zapalnych oraz liczbę limfocytów śród nabłonkowych (*intraepithelial lymphocytes* – IEL). Za pomocą badania immunohistochemicznego z zastosowaniem przeciwciał monoklonalnych anty-CD3+ zidentyfikowano limfocyty CD3⁺. Ocenę biopatów z dwunastnicy w kierunku celiakii wykonano zgodnie z klasyfikacją Marsha.

Wyniki: U chorych na celiakię, zarówno nieleczonych, jak i leczonych dietą bezglutenową, obserwowano wzrost IEL, jednak ich liczba była znamienne większa u chorych niestosujących diety bezglutenowej. Limfocytarne zapalenie żołądka rozpoznano u 8,6% chorych na celiakię. Osoby te podawały nasilone dolegliwości dyspeptyczne. W badaniu immunohistochemicznym wykazano obecność nacieków limfocytów T CD3⁺ zarówno w biopatach błony śluzowej żołądka, jak i części pozaopuszkowej dwunastnicy.

Wnioski: Zmiany morfologiczne błony śluzowej żołądka należą do obrazu gastroenteropatii glutenowej. Mogą im towarzyszyć objawy dyspeptyczne, nietypowe w tej chorobie. Autorzy proponują rozważenie pobierania wycinków z części pozaopuszkowej dwunastnicy u chorych z objawami dyspeptycznymi.

Introduction

Celiac disease (gluten enteropathy) is a chronic inflammatory disease of the gastrointestinal (GI) tract of autoimmune aetiology, occurring in genetically predisposed persons. Hallmarks of celiac enteropathy include an early rise of intestinal intraepithelial lymphocytes (IEL), followed by crypt hyperplasia and villous atrophy, in response to oral gluten intake [1].

Inflammatory lesions in the GI tract of celiac patients seem not to be confined to the small intestine. Gluten enteropathy may be a risk factor of development of lymphocytic gastritis (LG) [2]. The diagnostic threshold for LG is usually taken as greater than 25 IEL per 100 gastric columnar epithelial cells [3]. The significance of mucosal gastric lesions in celiac patients and their influence on clinical course remain unexplained.

Aim

The aim of the studies was to evaluate the frequency of histological lesions in the gastric mucosa in celiac patients, including the presence of CD3⁺ lymphocytes and their influence on the clinical picture of gluten enteropathy.

Table I. Characteristics of patients with celiac disease and dyspepsia

Tabela I. Charakterystyka grup chorych na celiakię i pacjentów z dyspepsią

Variable	Celiac disease, n	Dyspepsia, n
Number	35	55
Age, min-max, mean \pm SD [years]	18-72 (30.8 \pm 8)	18-72 (41 \pm 7)
Women	20	29
Men	15	26
CD not treated with GFD	24	48 – Dyspepsia
CD treated with GFD	11	7 – DU
Coexistent diseases	2 – S Hashimoto 3 – UC 1 – L-Crohn D	1 – UC

CD – celiac disease, GFD – gluten-free diet, DU – duodenal ulcer, S Hashimoto – Hashimoto struma, UC – ulcerative colitis, L-Crohn D – Crohn's disease

CD – celiakia, GFD – dieta bezglutenowa, DU – choroba wrzodowa dwunastnicy, S Hashimoto – wole Hashimoto, UC – wrzodziejące zapalenie jelita grubego, L-Crohn D – choroba Leśniowskiego-Crohna

Material and methods

Patients from the Outpatient Clinic of the Department of Gastroenterology and Hepatology Jagiellonian University in Krakow, suffering from symptoms indicating malabsorption syndrome or dyspeptic symptoms, as well as patients with previously diagnosed celiac disease, were included in the study.

They were informed about the subject of the above studies and expressed written consent to the studies. Clinical investigation comprised history of disease, including present complaints indicating celiac disease, such as diarrhoea, microcytic anaemia, as well as dyspeptic symptoms including epigastric discomfort, early satiety, belching or nausea and physical examination.

Venous blood probes were taken for evaluation of the blood count, iron level and the titre of anti-transglutaminase (tTG) IgA antibodies in the serum.

Upper GI tract endoscopy was performed for the evaluation of macroscopic lesions in the mucosa as well as for taking mucosal biopsies from the body and antral part of the stomach and the distal part of the duodenum. Also the urease test for *Helicobacter pylori* bacteria presence in the gastric mucosa was performed.

The diagnosis of celiac disease was based on the clinical symptoms, evaluation of tTG IgA in the serum and histological assessment of the distal part of the duodenal mucosa. Patients with infections of the GI tract, treated with non-steroidal anti-inflammatory drugs (NSAID) or glucocorticoids were excluded from the study.

Finally 90 patients, aged 18-72 years (average: 30.8 \pm 4.5 years), including 35 celiac patients (n = 24, patients with recent diagnosis of CD, n = 11, patients with earlier diagnosis of CD) and 55 patients presenting dyspeptic symptoms (n = 48, patients without significant lesions in the gastric and duodenal mucosa, n = 7 with duodenal ulcers) as the control group were included. Additionally, in 6 celiac patients and 1 in the control group, coexistence of autoimmune disorders was detected. Characteristics of examined groups are presented in Table I.

In the celiac patients, a strict gluten-free diet was recommended. In patients with dyspeptic symptoms, a standard dose of proton pump inhibitor (PPI) was initiated.

Celiac patients with LG underwent upper GI endoscopy after 6 months of gluten-free diet therapy, with

biopsies being taken from the stomach and distal part of the duodenum for evaluation of the intensity of mucosal lymphocytic infiltrates.

Histological evaluation

Histological evaluation of mucosal lesions in the gastric mucosa stained with haematoxylin-eosin was performed according to the Sydney system, including normal appearance of gastric mucosa, chronic superficial gastritis (activity 0-3), follicular gastritis and atrophic gastritis [2].

The presence of *H. pylori* in the gastric mucosa was evaluated in the gastric mucosa biopsies, stained with haematoxylin-eosin and modified Giemsa method.

Histology of the mucosa of the distal part of the duodenum was expressed according to the Marsh classification, including: normal mucosa, type I: infiltrative lesions with more than 30 lymphocytes/100 epithelial cells, type II: infiltrative/hyperplastic lesions, type III: subdivided into partial (IIIA), subtotal (IIIB) and total (IIIC) villous atrophy [2, 4]. Type III is considered as the most characteristic for coeliac disease [4, 5].

Evaluation of the number of IEL in the biopsies from the body, antral part of the gastric mucosa and distal part of the duodenum stained with haematoxylin-eosin was performed. Five hundred consecutive epithelial cells were examined. The number of lymphocytes per 100 epithelial cells was counted. Lymphocytic gastritis was said to be present when the number of mature intra-epithelial lymphocytes was more than 25/100 gastric columnar epithelial cells [3].

For the identification of lymphocytes forming infiltrates in the gastric mucosa and the distal part of the duodenum, immunostaining was performed. Anti-CD3+ monoclonal antibodies (pan T cell marker) (Dako,

High Wycombe, UK) at 1 in 50 dilution were used according to the method described by the producer.

Statistical analysis

Statistical analysis was performed using the program Statistica 8.0 (UJ license). Results were expressed as means \pm SEM. Statistical differences between examined groups were evaluated with the χ^2 test. Differences at the level of $p < 0.05$ were considered significant.

Results

Clinical picture of patients with gluten enteropathy

Among dyspeptic symptoms observed in the coeliac patients, early satiety in the epigastrium was observed more frequently in comparison with the control group, but the differences were not statistically significant (Table II).

In patients diagnosed with endoscopy because of dyspeptic complaints, symptoms indicating coeliac disease, such as diarrhoea (45% of cases), microcytic anemia (35% of cases), osteoporosis (9% of cases), loss of weight (20% of cases), as well as depression (4% of cases) were reported (Figure 1).

Endoscopic picture of gastric mucosa in patients with gluten enteropathy

Gastric mucosa in the coeliac patients as well as in the control group showed focal reddening and erosions in the antral part and in the distal part of the duodenum.

Lymphocytic gastritis

In the coeliac patients, both treated and not treated with a gluten-free diet, increase of the number of IEL was observed in the gastric mucosa. The mean IEL num-

Table II. Frequency of clinical symptoms in the examined groups of patients

Tabela II. Częstość występowania objawów klinicznych w badanych grupach

Symptoms	Groups of patients			
	A (n = 28)	B (n = 7)	C (n = 33)	D (n = 22)
Epigastric satiety	12 (45%)	3 (43%)	14 (42%)	9 (41%)
Belching	6 (22%)	2 (28%)	3 (9%)	4 (17%)
Epigastric pain/discomfort	14 (50%)	3 (43%)	14 (42%)	10 (45%)
Nausea	6 (21%)	2 (28%)	6 (18%)	5 (23%)
Pyrosis	7 (25%)	1 (14%)	7 (21%)	6 (27%)
Diarrhoea	19 (68%)	4 (57%)	5 (15%)	4 (18%)

A – coeliac disease and *H. pylori* infection, B – coeliac disease without *H. pylori* infection, C – dyspepsia and *H. pylori* infection, D – dyspepsia without *H. pylori* infection

A – z celiakią i infekcją *H. pylori*, B – z celiakią bez infekcji *H. pylori*, C – z dyspepsją czynnościową i infekcją *H. pylori*, D – z dyspepsją czynnościową bez infekcji *H. pylori*

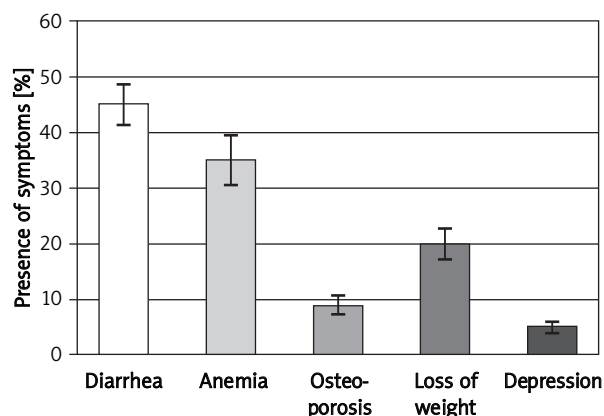


Fig. 1. Presence of symptoms indicating malabsorption syndrome in patients with dyspepsia or reflux disease, examined with endoscopy

Ryc. 1. Występowanie symptomów wskazujących na zespół upośledzonego wchłaniania u chorych, którym wykonano endoskopię z powodu objawów dyspeptycznych lub refluksowych

ber in the gastric mucosa of patients not treated with the gluten-free diet was 9.2 ± 0.5 and it was significantly higher than the IEL number in the control group (4.2 ± 0.4) ($p < 0.05$) (Table III).

Three coeliac patients (8.6% of cases) and one in the control group fulfilled criteria of LG, which means that the IEL number exceeded 25 per 100 epithelial cells (Table III).

In all these cases, coeliac disease was diagnosed for the first time. Patients with gluten enteropathy and diagnosed LG suffered from intensive dyspeptic symptoms, mainly epigastric pain or discomfort, nausea, and pyrosis. Also, symptoms indicating malabsorption, such as microcytic anaemia, loss of weight or diarrhoea, were

observed (Table IV). Endoscopic evaluation revealed focal reddening and mosaic structure in the body or antral part of the gastric mucosa (Figures 2 A, B). Thinning of the circular folds and mosaic surface of the distal part of the duodenum was also observed (Figure 2 C).

Haematoxylin-eosin staining revealed lymphocytes in the superficial epithelium and in the gastric foveolae of the body and antral part of the stomach, proportion from 1 : 3 to 1 : 2, focal 1 : 1 (Figures 3 A, 4 A).

Lymphocytic gastritis in the coeliac patients coexisted with partial (1 patient) or total villous atrophy (2 patients) in the distal part of the duodenum, according to grade III B and III C of the Marsh scale respectively (Figures 5 A, 6 A).

Helicobacter pylori infection was detected in one patient in this group. In addition, gastric mucosal lesions corresponding with LG were found in one patient presenting dyspeptic symptoms from the control group, with previously diagnosed ulcerative colitis.

Immunohistology showed in patients with LG the presence of CD3⁺ T lymphocytes, both in the gastric mucosa and in the distal part of the duodenum mucosal biopsies, giving evidence for the connection of lesions observed in the stomach and the duodenum in coeliac disease (Figures 3 B, 4 B, 5 B, 6 B).

Application of the gluten-free diet in the coeliac patients with LG caused the disappearance of dyspeptic symptoms, not responding to the previous PPI treatment. In 2 cases a decrease of IEL number in the gastric mucosa in the control histological evaluation after 6 months was observed.

Discussion

Association of coeliac disease with histological lesions in the gastric mucosa has not been fully explained. The results of our studies revealed the presence of LG in 8.6% of coeliac patients.

Table III. Histological lesions in the gastric mucosa in coeliac patients and controls

Tabela III. Zmiany histopatologiczne w błonie śluzowej żołądka u chorych na celiakię i w grupie kontrolnej pacjentów z dyspepsją

Lesions	Groups of patients		
	CD (n = 35)		Dyspepsia (n = 55)
	Not treated with GFD	Treated with GFD	
Normal gastric mucosa	0		0
Chronic superficial gastritis	16 (67%)	5 (55%)	38 (69%)
Mean IEL in the gastric mucosa	9.2 ± 0.5	6.3 ± 0.4	$4.2 \pm 0.4\%$
LG	3 (8.6%)		1 (1.8%)
<i>Helicobacter pylori</i> infection	7 (20%)	0	30 (55%)

CD – coeliac disease, GFD – gluten-free diet, LG – lymphocytic gastritis

CD – celiakia, GFD – dieta bezglutenowa, LG – limfocytarne zapalenie żołądka

Table IV. Results of clinical and histological studies in patients with coeliac disease and dyspepsia with lymphocytic gastritis**Tabela IV.** Wyniki badań klinicznych i histopatologicznych u chorych na celiakię lub z dyspepsją, z limfocytarnym zapaleniem błony śluzowej żołądka

Patient	Age/sex	Symptoms	Endoscopic lesions	Histology of gastric mucosa	<i>Helicobacter pylori</i>	Histology of duodenal mucosa	Coexisting diseases
1	57/F	Abdominal pain, diarrhoea, loss of weight	Reddening, mosaic surface	Chronic gastritis, non-active, moderate degree, focal pancreatic metaplasia	0	Marsh III C	0
2	33/F	Epigastric pain, pyrosis, anaemia	Reddening, mosaic surface	Chronic gastritis, non-active, moderate degree	0	III C	0
3	28/M	Epigastric discomfort, Nausea, anaemia	Reddening, antral erosions	Chronic gastritis, non-active, foveolar hyperplasia	+	III B	Hashimoto struma
4	41/M	Epigastric discomfort	Reddening	Chronic gastritis, low degree	+	Normal	UC

F – female, M – male, UC – ulcerative colitis

F – kobieta, M – mężczyzna, UC – wrzodzące zapalenie jelita grubego

All coeliac patients with LG were not treated with the gluten-free diet previously and presented symptoms of malabsorption as well as dyspeptic complaints, making the main indication for the diagnosis of the upper GI tract. The results of our studies are similar to the data of 10% frequency of LG in coeliac patients, reported by Feeley *et al.* [3]. The results of other authors were divergent

and ranged from 4% to 38% frequency of LG in coeliac patients [6, 7]. Dyspeptic symptoms were also reported by Usai *et al.* [8]. They could originate from formation of lymphocytic infiltrates, followed by impairment of the gastric mucosal barrier and gastric functional disorder.

Clinical symptoms were accompanied by non-specific endoscopic lesions in the gastric mucosa, such as

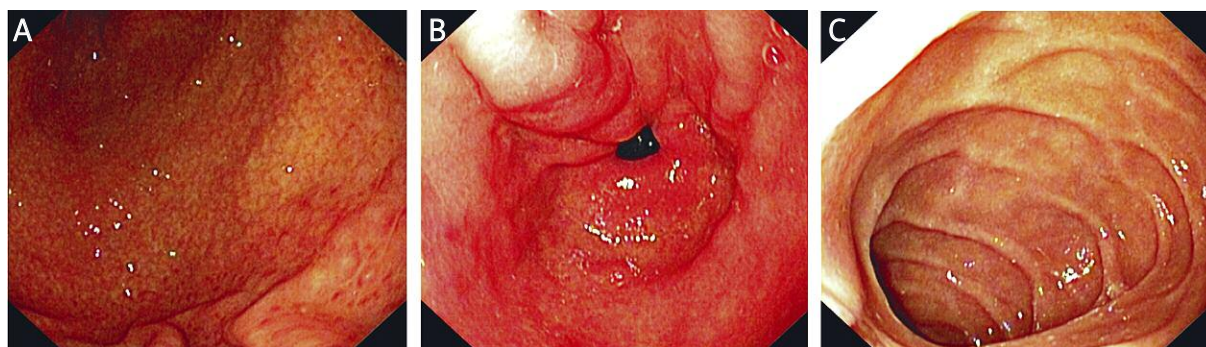


Fig. 2. **A** – Endoscopic picture of the body of the stomach in patients with diagnosed coeliac disease and lymphocytic gastritis. Reddening and mosaic surface of the mucosa. **B** – Endoscopic picture of the antral part of the stomach in patients with diagnosed coeliac disease and lymphocytic gastritis. Reddening and the fold deforming pyloric region. **C** – Endoscopic picture of the distal part of the duodenum in patients with diagnosed coeliac disease. Thinning of the circular folds and mosaic surface of the distal part of the duodenum

Ryc. 2. **A** – Obraz endoskopowy trzonu żołądka u chorego na celiakię i z rozpoznaniem limfocytarnym zapaleniem żołądka. Zaczerwienienie i mozaikowa powierzchnia błony śluzowej. **B** – Obraz endoskopowy części antralnej żołądka u chorego na celiakię i z rozpoznaniem limfocytarnym zapaleniem żołądka. Dwubarwność błony śluzowej i fałd deformujący odźwiernik. **C** – Obraz endoskopowy części pozaopuszkowej dwunastnicy. Ścieńczenie fałdów okrężnych błony śluzowej. Zaznaczona mozaikowa powierzchnia błony śluzowej części pozaopuszkowej dwunastnicy

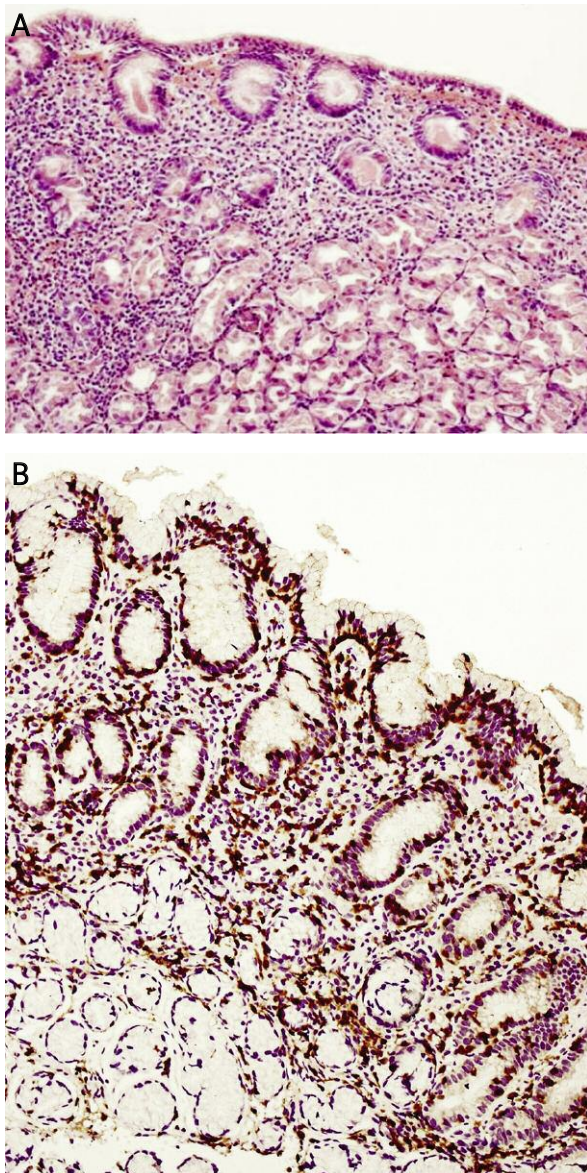


Fig. 3. A – Histological changes in the body of the stomach. Haematoxylin-eosin staining. Lymphocytic gastritis. Lymphocytes in the superficial epithelium and in the gastric foveolae of the body of the stomach, proportion 1 : 3, focal 1 : 1. **B** – Immunohistochemical reaction in the body of the gastric mucosa. CD3+ lymphocytic infiltrates

Ryc. 3. A – Zmiany histopatologiczne w błonie śluzowej trzonu żołądka. Barwienie hematoksyliną i eozyną. Limfocytarne zapalenie żołądka. Limfocyty w nabłonku powierzchni i dołeczkach błony śluzowej trzonu żołądka w proporcji 1 : 3, ogniskowo 1 : 1. **B** – odczyn immunohistochemiczny w błonie śluzowej trzonu żołądka. Nacieki limfocytów CD3+

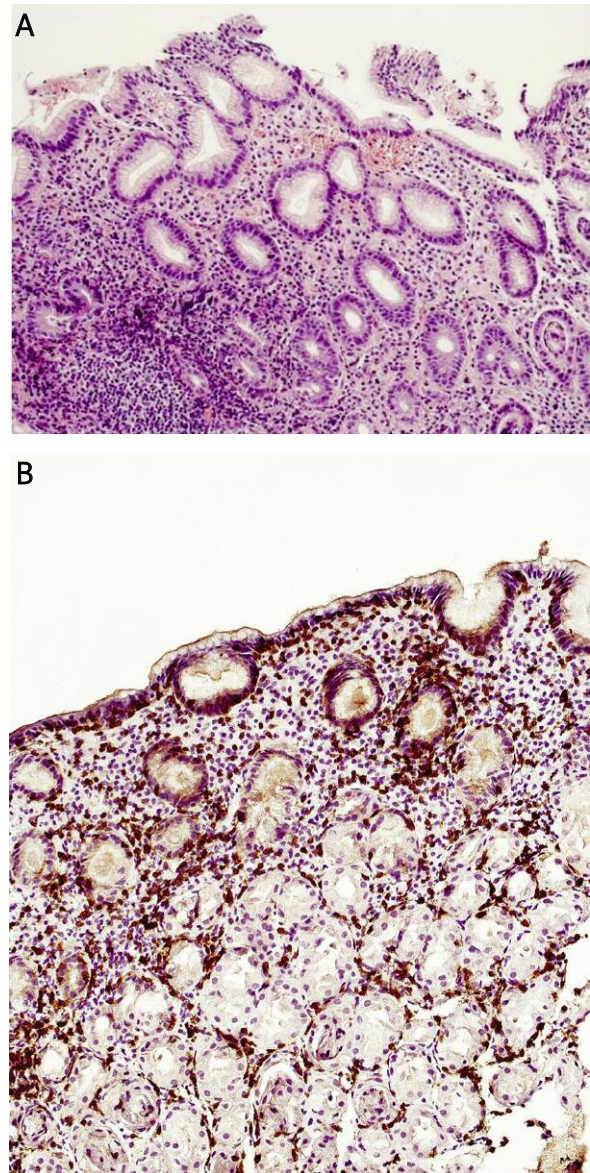


Fig. 4. A – Histological changes in the antral part of the gastric mucosa. Haematoxylin-eosin staining. Lymphocytic gastritis. Lymphocytes in the superficial epithelium and in the gastric foveolae of the body of the stomach, proportion 1 : 2, focal 1 : 1. **B** – Immunohistochemical reaction in the antral part of the gastric mucosa. CD3+ lymphocytic infiltrates

Ryc. 4. A – Zmiany histopatologiczne w błonie śluzowej okolicy antralnej żołądka. Barwienie hematoksyliną i eozyną. Limfocytarne zapalenie żołądka. Limfocyty w nabłonku powierzchni i dołeczkach błony śluzowej trzonu żołądka w proporcji 1 : 2, ogniskowo 1 : 1. **B** – Odczyn immunohistochemiczny w błonie śluzowej okolicy antralnej żołądka. Nacieki limfocytów CD3+

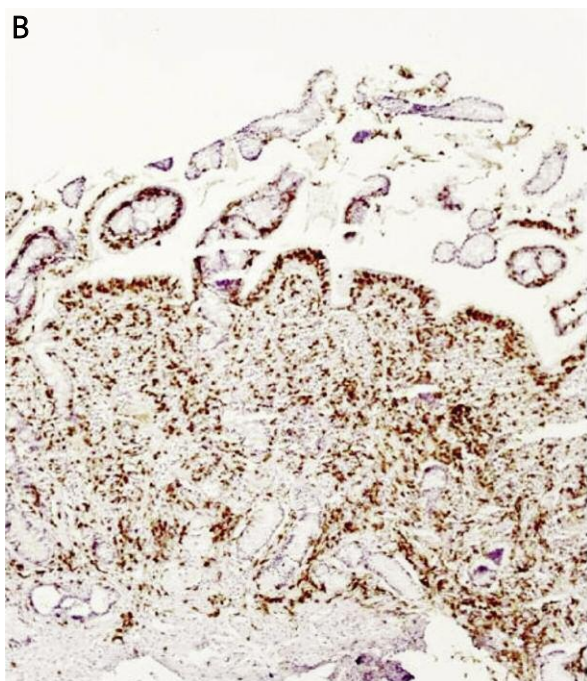
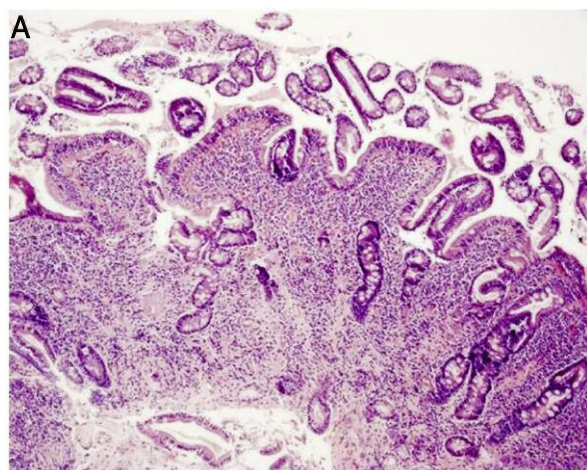


Fig. 5. A – Histological changes in the mucosa of the distal part of the duodenum (Marsh III B). Haematoxylin-eosin staining. Partial villous atrophy. CD3+ lymphocytic infiltrates. **B** – Immunohistochemical reaction in the mucosa of the distal part of the duodenum. Partial villous atrophy. CD3+ lymphocytic infiltrates

Ryc. 5. A – Zmiany histopatologiczne w błonie śluzowej części pozaopuszkowej dwunastnicy. Barwienie hematoksylina i eozyną. Częściowy zanik kosmków jelitowych (stopień III B według Marsha). Widoczne nacieki limfocytarne. **B** – Odczyn immunohistochemiczny w błonie śluzowej części pozaopuszkowej dwunastnicy. Częściowy zanik kosmków jelitowych. Nacieki limfocytów CD3+

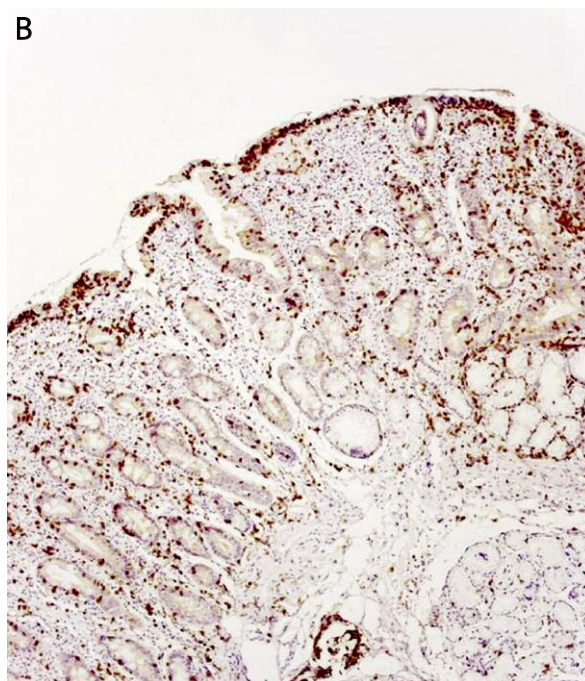
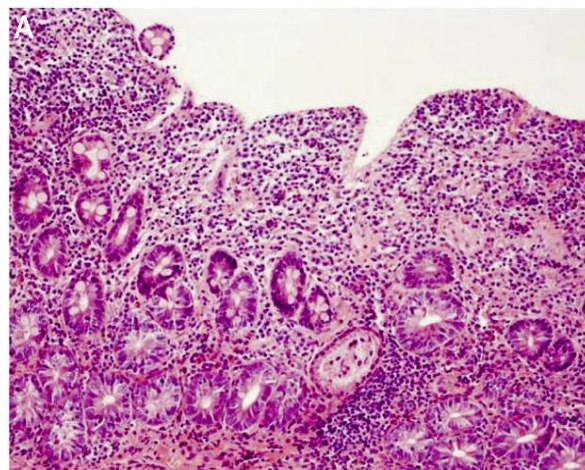


Fig. 6. A – Histological changes in the mucosa of the distal part of the duodenum. Haematoxylin-eosin staining. Total villous atrophy (Marsh III C). CD3+ lymphocytic infiltrates. **B** – Immunohistochemical reaction in the mucosa of the distal part of the duodenum. Total villous atrophy. CD3+ lymphocytic infiltrates

Ryc. 6. A – Zmiany histopatologiczne w błonie śluzowej części pozaopuszkowej dwunastnicy. Barwienie hematoksylina i eozyną. Całkowity zanik kosmków jelitowych (stopień III C według Marsha). Widoczne nacieki limfocytarne. **B** – Odczyn immunohistochemiczny w błonie śluzowej części pozaopuszkowej dwunastnicy. Całkowity zanik kosmków jelitowych. Nacieki limfocytów CD3+

reddening, mosaic surface or erosions. Mucosal lesions typical for LG, such as gastritis varioliformis, including aphthoid erosions, papular lesions or thickening of mucosal folds, described by other authors, were not observed in our patients [3].

In all examined coeliac patients, an increased number of IEL was observed, but did not fulfil the criterion of LG with the exception of 3 cases. The increased number of IEL could be the result of the autoimmune reaction in the course of coeliac disease or the direct contact of gluten with the mucosal barrier in the stomach in persons with hypersensitivity to this antigen [3, 6]. Immunohistology of the gastric and duodenal mucosa biopsies revealed that lymphocytic infiltrates in both regions were formed by CD3⁺ T lymphocytes, suggesting that coeliac disease is an example of diffuse T lymphocyte gastroenteropathy.

As previous results revealed, LG could be the manifestation of *H. pylori* infection [9]. The results of our studies showed the frequency of *H. pylori* in the gastric mucosa of coeliac patients and in the control group as 20% and 55% respectively, which was lower than the results reported by other authors, 82% and 97% respectively [2].

The explanation for lower *H. pylori* frequency in the examined group could be successful eradication therapy performed in patients with relapsing dyspeptic symptoms.

The above study showed the presence of LG in the coeliac patients, with or without *H. pylori* infection, which may suggest that these bacteria and the gluten enteropathy are independent factors inducing the rise of IEL number in the gastric mucosa. Application of the gluten-free diet caused regression of dyspeptic symptoms, accompanied by a fall of the IEL number in the gastric mucosa, in the control histological evaluation after 6 months. It suggests the significant role of lymphocytic infiltrates in the gastric mucosa in inducing dyspeptic symptoms in the coeliac patients.

In one dyspeptic patient from the control group, fulfilling the criterion of LG, ulcerative colitis was diagnosed previously. The association between LG and ulcerative colitis could be explained by the involvement of Th2 lymphocytes in the immunological response with the subsequent IL-5 and IL-10 cytokine mucosal expression [10].

A full explanation of the role of histological lesions in the gastric mucosa needs further studies in a more numerous group of patients.

Conclusions

Lymphocytic gastritis including CD3⁺ T lymphocytes in the gastric and the distal part of duodenal mucosa belongs to the picture of gluten enteropathy. Dyspeptic

symptoms, observed in some of the coeliac patients, besides typical symptoms indicating malabsorption syndrome, may have an association with intraepithelial lymphocytosis. Taking biopsies from the distal part of the duodenum, from patients presenting dyspeptic symptoms, during gastroscopy, may contribute to the diagnosis of coeliac disease in some of them.

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